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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,156	12/05/2003	Shaomeng Wang	UM-08477	1029

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,156	WANG ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,27-41,43-47,49,50,52-55,60,61,78-80,82-93 and 96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *46,47,49 and 50* is/are allowed.

6)☒ Claim(s) *1,2,27-41,43-45,52-55,60,61,78-80,82-93 and 96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-23-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 2, 2007 has been entered.

The outstanding rejection under 35 USC 112, first paragraph is withdrawn in view of the applicant's remarks filed April 2, 2007. Apogossypol is having anticancer activity according to Becattini et al. Moreover, Sheeley et al. does not teach ethylgossypol as being ineffective against tumor cell lines. In fact, Shelley et al. does not discuss ethylgossypol and its antitumor activity since the gossypol derivative having ethyl moiety disclosed in page 214, col. 2, is not directed to ethylgossypol.

Claims 1, 2, 27-41, 43-47, 49-50, 52-55, 60-61, 78-80, 82-93, and 96 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 27-41, 43-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the cancers demonstrated in the

examples in the instant specification, does not reasonably provide enablement for other hyperproliferative diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to provide information allowing the skilled artisan to ascertain these compounds possessing the recited, and claimed, physiological activity without undue experimentation.

(1) **The nature of the invention**

All of the rejected claims are drawn to an invention which pertains to a method of treating all hyperproliferative diseases with the herein recited gossypol compounds. The nature of the invention is complex in that it encompasses the treatment of all types of hyperproliferative diseases including all types of tumors.

(2) **Breadth of the Claims**

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass inhibition of any number of hyperproliferative diseases including all types of tumors by the herein claimed gossypol compounds.

(3) **Guidance given by the instant specification**

The guidance given by the specification as to how one would administer the herein claimed compounds to a subject in order to inhibit any type of tumor growth is limited. All of the guidance provided by the specification is directed toward the possibilities of treating tumor by modulate Bcl-2 family protein expression (See the instant specification, page 57-58 for example). It is not clear if all of the known hyperproliferative diseases are overly expressing Bcl-2 family proteins or that gossypol compounds can treat all types of tumors and all types of hyperproliferative diseases.

(4) **Working Examples**

There is only limited number of working example disclosed in the instant specification.

(5) **State of the Art**

While the state of the art is relatively high with regard to treating specific cancers or tumors, the state of the art with regard to treating cancer or tumor generally is underdeveloped. In particular, there is no known anticancer agent which is effective against all cancers. Carter et al. (Chemotherapy of Cancer 2nd ed 1981) clearly teaches that for the forty known anticancer agents, none are effective against all cancers (pages 362-365). There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-I), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect a single organ are often not generally treatable. For example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

(6) **Predictability of the Art**

The invention is directed to treating hyperproliferative diseases in general. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). Cancers are especially unpredictable due to their complex nature. Please refer to the discussion of Carter, et al. and the state of the art in (5) that shows the different treatments of cancers. The treatment of one type of cancer or tumor could not be necessarily the same for the other type. Furthermore, in Johnson et al., British Journal of Cancer, 2001; 84(10):1424-1431, it states that there is no good *in vitro* model, predictor or indicator for all tumor types. In the instant specification, only *in vitro* data are set forth. Accordingly, the predictability for employing the instant gossypol compounds for treating all kinds of hyperproliferative diseases is relatively low and unpredicatable.

(7) **The Quantity of Experimentation necessary**

In order to practice the claimed invention, one of skill in the art would have to first envision a combination of an appropriate pharmaceutical carrier, a dosage for each compound, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the combination in the model system to determine whether or not the combination is effective for inhibiting cancer cells. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of cancer with any herein claimed compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical

compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of cancer with any compound, the entire, unpredictable process would have to be repeated until successful. In order to practice Applicant's invention, it would be necessary for one to conduct the preceding experimentation for each type of cancer or hyperproliferative disease because, as described by Carter, et al., there is no known drug effective for inhibiting all types of cancer, let alone all hyperproliferative disease. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to inhibit cancer cells in a mammal by administration of one of the compounds within the claims.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, a method for inhibiting tumor growth generally by administering the herein claimed various gossypol compounds is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52-55, 60-61, 78-80, 82-93, and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,114,397 ('397) from IDS filed October 17, 2005 in view of Merck Manual of Diagnosis and Therapy, 16th ed., 1992, pages 1275-1277.

'397 teaches a method and composition of employing gossypol, gossypol acetic acid, gossypolone and metabolites as effective in treating cancer (See for example the abstract and claims 1-14). '397 also teaches gossypol can be combined with other anti-

cancer therapeutic agents such as cisplatin in a method and composition of treating cancer (see abstract and col. 2, line 65 - col. 3, line 11).

'397 does not expressly teach the use of radiation in combination with gossypol compounds to treat cancer. '397 does not expressly teach the herein recited regimen of the compounds used such as route of administrations and the sequence of administration. '397 does not expressly teach the method of treating cancer employs the optical isomers gossypol compounds.

Merck Manual teaches that radiation is one of the common modalities in cancer treatment (See page 1276-1277).

It would have been obvious to one of ordinary skill in the art at the time of invention to employ both radiation and gossypol compounds of '397, as racemic or pure enantiomers, in a method and composition of treating cancer. It would have been obvious to one of ordinary skill in the art at the time of invention to optimize the therapeutic regimen of the cancer treatment employing the gossypol compounds and radiation.

One of ordinary skill in the art would have been motivated to employ both radiation and gossypol compounds of '397, as racemic or pure enantiomers, in a method and composition of treating cancer. Since both radiation and gossypol compounds of '397 are known to be useful in treating cancer individually, combining them in a composition or concomitantly employing them in a method of treating the very same disease (i.e., cancer) would be prima facie obvious, at least additive effect would be expected. '397 teaches a chiral center in the claimed compound, and illustrated

separation for such optical isomers. It is well settled patent law that the skilled artisan, knowing a compound contains an asymmetric carbon atom, possesses all resultant optical isomers. The skilled artisan in possession of the designated compounds, possesses all isomeric forms of the compound for the old and well known antitumor utility. It is well known in the pharmaceutical art that various optical isomers will exhibit biological effects at various levels. Absent some difference in kind between the various isomers the skilled artisan would have seen each isomer as *prima facie* obvious (see *In re Adamson and Duffin*, 125 USPQ 233 (CCPA 1960)). The skilled artisan would have expected optical isomers to be separable and isomers so separated to exhibit physiological effects at varying levels. Possessing a compound known to contain chiral centers, places all the resultant compounds in the skilled artisan's possession. It would follow therefore, the instant claims recite *prima facie* obvious subject matter and are properly rejected under 35 USC 103.

One of ordinary skill in the art would have been motivated to optimize the therapeutic regimen of the cancer treatment employing the gossypol compounds and radiation since optimization of the resulted parameters (e.g., dosage and regimen) is routinely done in the art and thus obvious as being within the purview of skilled artisan.

Examiner notes that the herein claimed mechanism of action of gossypol must be present in the method suggested by the cited prior arts since the products and its intrinsic properties cannot be separated.

Response to Arguments

Applicant's arguments filed April 2, 2007 averring the presence of unexpected synergism have been fully considered but they are not persuasive. As discussed in the previous office action, it is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, the alleged synergistic effect are not seen in all cases: for example, in Fig.16, the Breast cancer cell survival rate for (-)-gossypol is similar to that of Taxol plus (-)-gossypol when the concentration of (-)-gossypol as above 10μM. Furthermore, the scope of the claim is much broader than what is demonstrated in the instant examples. For example, the examples in the specification are limited to only (-)-gossypol and not other gossypol derivatives. The cancer cell lines are also limited to a few tumor cell lines. The secondary agents are essentially limited to taxol. However, the scope of the instant claims encompassed far more than what is disclosed in the specification. Accordingly, the examples in instant specification are not commensurate with the scope of subject matter claimed. Furthermore, in some cases, no synergism is seen. Therefore, the instant claims are still considered to be properly rejected under 35 USC 103(a).

Allowable Subject Matter

Claims 46-47, 49 and 50 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1617